UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Note to Reader
January 15, 1998

Background: As part of its effort to involve the public in the implementation of the Food Quality Protection Act of 1996 (FQPA), which is designed to ensure that the United States continues to have the safest and most abundant food supply. EPA is undertaking an effort to open public dockets on the organophosphate pesticides. These dockets will make available to all interested parties documents that were developed as part of the U.S. Environmental Protection Agency's process for making reregistration eligibility decisions and tolerance reassessments consistent with FQPA. The dockets include preliminary health assessments and, where available, ecological risk assessments conducted by EPA, rebuttals or corrections to the risk assessments submitted by chemical registrants, and the Agency's response to the registrants' submissions.

The analyses contained in this docket are preliminary in nature and represent the information available to EPA at the time they were prepared. Additional information may have been submitted to EPA which has not yet been incorporated into these analyses, and registrants or others may be developing relevant information. It's common and appropriate that new information and analyses will be used to revise and refine the evaluations contained in these dockets to make them more comprehensive and realistic. The Agency cautions against premature conclusions based on these preliminary assessments and against any use of information contained in these documents out of their full context. Throughout this process, If unacceptable risks are identified, EPA will act to reduce or eliminate the risks.

There is a 60 day comment period in which the public and all interested parties are invited to submit comments on the information in this docket. Comments should directly relate to this organophosphate and to the information and issues available in the information docket. Once the comment period closes, EPA will review all comments and revise the risk assessments, as necessary.

These preliminary risk assessments represent an early stage in the process by which EPA is evaluating the regulatory requirements applicable to existing pesticides. Through this opportunity for notice and comment, the Agency hopes to advance the openness and scientific soundness underpinning its decisions. This process is designed to assure that America continues to enjoy the safest and most abundant food supply. Through implementation of EPA's tolerance reassessment program under the Food Quality Protection Act, the food supply will become even safer. Leading health experts recommend that all people eat a wide variety of foods, including at least five servings of fruits and vegetables a day.

Note: This sheet is provided to help the reader understand how refined and developed the pesticide file is as of the date prepared, what if any changes have occurred recently, and what new information, if any, is expected to be included in the analysis before decisions are made. **It is not meant to be a summary of all current information regarding the chemical.** Rather, the sheet provides some context to better understand the substantive material in the docket (RED chapters, registrant rebuttals, Agency responses to rebuttals, etc.) for this pesticide.

Further, in some cases, differences may be noted between the RED chapters and the Agency's comprehensive reports on the hazard identification information and safety factors for all organophosphates. In these cases, information in the comprehensive reports is the most current and will, barring the submission of more data that the Agency finds useful, be used in the risk assessments.

Jack E. Housenger, Acting Director
Special Review and Reregistration Division

MEMORANDUM

SUBJECT: RfD/Peer Review Report of Methidathion

CASRN. 950-37-8
EPA Chem. Code: 100301
Caswell No. 378B

FROM: George Z. Ghali, Ph.D.
Manager, RfD/Quality Assurance Peer Review
Health Effects Division (H7509C)

TO: Dennis Edwards, PM 19
Insecticide-Rodenticide Branch
Registration Division (H7505C)

Lois Rossi, Chief
Reregistration Branch
Reregistration and Special Review Division (H7508W)

The Health Effects Division RfD/Peer Review Committee met on March 25, 1993 to evaluate the existing toxicology data in support of Methidathion re-registration and to re-reassess the Reference Dose (RfD) for this chemical.

The RfD for this chemical was first assessed by the Health Effects Division RfD Committee on October 30, 1987 and verified by the Agency RfD Work Group on January 30, 1988. At that time the RfD was based on a no-observable effect level (NOEL) of 4 ppm (0.15 mg/kg/day) for elevated hepatic enzymes, gross hepatic lesions, chronic hepatitis and depression of cholinesterase activity of the red blood cells observed at 40 ppm (1.33 mg/kg/day) in a long-term toxicity study in dogs. An Uncertainty Factor (UF) of 100 was used to account for the inter-species extrapolation and intra-species variability. On this basis the RfD was calculated to be 0.0015 mg/kg/day. It should be noted that a regulatory value of 0.005 mg/kg/day was established for this chemical by the World Health Organization in 1975. The RfD/Peer Review Committee recommended that the RfD, as established by the RfD Peer Review Committee in 1987 and verified by the Agency RfD Work Group in 1988, remain unchanged.

The Committee considered the chronic toxicity study in rats (83-1a), the long-term toxicity study in dogs (83-1b), the developmental toxicity studies in rats and rabbits (83-3a and -3b) and the reproductive toxicity study in rats (83-4) to be acceptable and the data evaluation records, except for minor revision as specified below, to be adequate.

Since the carcinogenicity issue had already been addressed by the Health Effects Division Carcinogenicity Peer Review Committee (CPRC), the carcinogenicity studies in rats and mice were not examined by the RfD Peer Review Committee. The chemical was classified by the CPRC as a "Group C" carcinogen. Quantification of potential human risk, using a low dose extrapolation model (Q^*_1), was also recommended.

There was no evidence, based on the available data, to suggest that the chemical was associated with significant reproductive or developmental toxicity.

A. Individual in Attendance

1. Peer Review Committee Members and Associates (Signature indicates concurrence with the peer review unless otherwise stated).

William Burnam _____

Reto Engler _____

Marcia Van Gemert _____

Karl Baetcke _____

Henry Spencer _____

William Sette _____

Roger Gardner _____

Stephen Dapson _____

George Ghali _____

Rick Whiting _____

2. Scientific Reviewer(s) (Committee or non-committee members
responsible for data presentation; signatures indicate technical accuracy of panel report).

Melba Morrow _____

Joycelyn Stewart _____

3. Others

Flora chow and N. Thoa of CCB/HED as observers

CC: Penny Fenner-Crisp
Richard Schmitt
Kerry Dearfield
Karl Baetcke

Joycelyn Stewart
Melba Morrow
Rick Whiting
James Kariya

B. Material Reviewed:

Material available for review by the Committee included data evaluation records for the chronic toxicity study in rats (83-1a), the long-term toxicity study in dogs (83-1b), the developmental toxicity studies in rats and rabbits (83-3a and -3b) and the reproductive toxicity study in rats (83-4) and the tox-one liner.
The Committee focused the discussion on the following studies:

1. Yau, E. et al. (1986). Methidathion: 2-year oral oncogenicity and toxicity study in albino rats. MRID No. 00160260, HED Doc. No. 005743.

Core Classification: Guideline

Committee's Conclusion and Recommendation:

The chemical was tested in Sprague-Dawley rats at 4, 40 and 100 ppm (equivalent to 0.2, 2.0 and 5.0 mg/kg/day). The NOEL/LOEL for systemic toxicity were considered to be 0.2 and 2.0 mg/kg/day based upon depression of plasma, red blood cell and brain cholinesterase activity. The Committee agreed with the reviewer's evaluation and interpretation of the data. Since the carcinogenicity issue had been already addressed by the Health Effects Division Carcinogenicity Peer Review Committee, the RfD Peer Review Committee did not discuss the carcinogenicity phase of the study. The study was considered to be acceptable and the data evaluation record was considered to be adequate. This study satisfies data requirement 83-1a of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in rats.

2. Chang, J. C. F and Walberg, J. (1991). One-year dietary toxicity in Beagle dogs. MRID No. 00160260, HED Doc. 005743.

Core Classification: Core-minimum data.

Committee's Conclusion and Recommendations:

The chemical was tested in Beagle dogs at 0.5, 2.5, 4.0, 40.0 and 140.0 ppm [equivalent to 0.02, 0.07, 0.15, (1.33 for males, 1.39 for females) and (4.51 for males, 4.90 for females) mg/kg/day]. The NOEL/LOEL for systemic toxicity were considered to be 4.0 and 40.0 ppm in both sexes based upon the elevation of hepatic enzymes, gross hepatic lesions and the microscopic presence of bile plugs, distended bile canaliculi and chronic hepatitis. The Committee agreed with the reviewer's evaluation and interpretation of the data. The study was considered to be acceptable and the data evaluation record was considered to be adequate. This study satisfies data requirement 83-1b of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in dogs.

3. Salamon, C. (1986). Two-generation reproduction study in rats. MRID No. 40079812, HED Doc. No. 006587.

Core Classification: Core-minimum data.

Committee's Conclusion and Recommendation:

The chemical was tested in Sprague-Dawley rats at 5, 25 and 50 ppm. The NOEL/LOEL for parental systemic toxicity were considered to be 5 and 25 ppm based upon tremors and decreased food consumption during lactation, and decreased relative and absolute ovarian weight. The NOEL/LOEL for reproductive toxicity were considered to be 5 and 25 ppm based upon a decreased mating index and a generalized indication of pup unthriftyness while nursing, characterized by decreased pup weight and an increased incidence of hypothermia with appearance of starvation. The Committee agreed with the reviewer's evaluation and interpretation of the data. The study was considered to be acceptable and the data evaluation record was considered to be adequate. This study satisfies data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in rats.

4. Infurna, R. (1987). A teratology study in rats. MRID No. 40079808, HED Doc. No.

Core Classification: Core- Minimum data.

Committee's Conclusion and Recommendations:

The chemical was tested in CD rats at 0.25, 1.0 and 2.25 mg/kg/day. The NOEL/LOEL for maternal toxicity were considered to be 1.0 and 2.25 mg/kg/day based upon decreased body weight and food consumption during the treatment period and cholinergic signs. The NOEL for developmental toxicity was considered to be

2.25 mg/kg/day, the highest dose level tested. The Committee agreed with the reviewer's evaluation and interpretation of the data. The study was considered to be acceptable and the data evaluation record was considered to be adequate. The Committee recommended the addition of more data tables, especially for cesarian data. This study satisfies data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.

5. Giknis, M. (1987). A teratology study in rabbits. MRID No. 40079810, HED Doc. No. 006385.

Core Classification: Core- Minimum data.

Committee's Conclusion and Recommendations:

The chemical was tested in New Zealand white rabbits at 2, 6 and 12 mg/kg/day. The NOEL/LOEL for maternal toxicity were considered to be 6 and 12 mg/kg/day based upon cholinergic signs of toxicity. The NOEL for developmental toxicity was considered to be 12 mg/kg/day, the highest dose level tested. The Committee agreed with the reviewer's evaluation and interpretation of the data. The study was considered to be acceptable and the data evaluation record was considered to be adequate. The Committee recommended the addition of more data tables to the data evaluation record to substantiate the conclusions made by the reviewer. This study satisfies data requirement 83-3b of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rabbits.

C. Conclusions and Recommendations

1. Reference Dose

The RfD for this chemical was first assessed by the Health Effects Division RfD Committee on October 30, 1987 and verified by the Agency RfD Work Group on January 30, 1988. At that time the RfD was based on a no-observable effect level (NOEL) of 4 ppm (0.15 mg/kg/day) for elevated hepatic enzymes, gross hepatic lesions, chronic hepatitis and depression of cholinesterase activity of the red blood cells observed at 40 ppm (1.33 mg/kg/day) in a long-term toxicity study in dogs. An Uncertainty Factor (UF) of 100 was used to account for the inter-species extrapolation and intra-species variability. On this basis the RfD was calculated to be 0.0015 mg/kg/day. It should be noted that a regulatory value of 0.005 mg/kg/day was established for this chemical by the World Health Organization in 1975. The RfD/Peer Review Committee recommended that the RfD, as established by the RfD Peer Review Committee in 1987 and verified by the Agency RfD Work Group in 1988, remains unchanged.

2. Data Base

The Committee considered the chronic toxicity study in rats (83-1a), the long-term toxicity study in dogs (83-1b), the developmental toxicity studies in rats and rabbits (83-3a and -3b) and the reproductive toxicity study in rats (83-4) to be acceptable and the data evaluation records, except for minor revision as specified below, to be adequate.

3. Carcinogenicity

Since the carcinogenicity issue had already been addressed by the Health Effects Division Carcinogenicity Peer Review Committee (CPRC), the carcinogenicity studies in rats and mice were not examined by the RfD Peer Review Committee. The chemical was classified by the CPRC as a "Group C" carcinogen. Quantification of potential human risk, using a low dose extrapolation model (Q^*_1), was also recommended.

4. Developmental and reproductive Toxicity

There was no evidence, based on the available data, to suggest that the chemical was associated with significant reproductive or developmental toxicity.